
Natural Killer Cell-Activating Receptor NKG2D Mediates Innate Immune Targeting of Allogeneic Neural Progenitor Cell Grafts.

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Authors: Lori K Phillips, Elizabeth A Gould, Harish Babu, Sheri M Krams, Theo D Palmer, Olivia M Martinez

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Public Summary:

Scientific Abstract:

Cell replacement therapy holds promise for a number of untreatable neurological or psychiatric diseases but the immunogenicity of cellular grafts remains controversial. Emerging stem cell and reprogramming technologies can be used to generate autologous grafts that minimize immunological concerns but autologous grafts may carry an underlying genetic vulnerability that reduces graft efficacy or survival. Healthy allogeneic grafts are an attractive and commercially scalable alternative if immunological variables can be controlled. Stem cells and immature neural progenitor cells (NPC) do not express major histocompatibility complex (MHC) antigens and can evade adaptive immune surveillance. Nevertheless, in an experimental murine model, allogeneic NPCs do not survive and differentiate as well as syngeneic grafts, even when traditional immunosuppressive treatments are used. In this study, we show that natural killer (NK) cells recognize the lack of self-MHC antigens on NPCs and pose a barrier to NPC transplantation. NK cells readily target both syngeneic and allogeneic NPC, and killing is modulated primarily by NK-inhibiting "self" class I MHC and NK-activating NKG2D-ligand expression. The absence of NKG2D signaling in NK cells significantly improves NPC-derived neuron survival and differentiation. These data illustrate the importance of innate immune mechanisms in graft outcome and the potential value of identifying and targeting NK cell-activating ligands that may be expressed by stem cell derived grafts.

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